## Remarks

Claims 1, 3, 4, 7, 9-11 and 22-24 are pending herein. By this Amendment, claims 1, 3, 4, 7, 9, 11, 22 and 24 have been amended, and claims 2, 5 and 21 have been cancelled.

Claim 1 has been amended in part to include the contents of cancelled claims 5 and 21 and a portion of claim 3. Claim 1 has been further amended to overcome an objection and a rejection under 35 U.S.C. §112 thereto. Claim 4 has been amended to be consistent with an amendment to claim 1. Claim 7 has been amended to include a portion of claim 24. Claim 9 has been amended to depend upon claim 1 rather than cancelled claim 3. Claim 11 has been amended to overcome an objection thereto. Claim 22 has been amended to depend upon claim 7 rather than cancelled claim 12.

In the Office Action, claims 10 and 11 are objected to; claims 1 and 11 are rejected under 35 U.S.C. §112, second paragraph; claim 1 is rejected under 35 U.S.C. §112, first paragraph; claims 1-5, 7, 9 and 21-24 are rejected under 35 U.S.C. §112, first paragraph; and claims 1-5, 7, 9-11 and 21-24 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,413,934 to Stayton et al. ("Stayton") in view of both WO 97/29114 to Wilbur et al. ("Wilbur") and U.S. Patent No. 5,491,097 to Ribi et al. ("Ribi").

In view of the amendments and remarks herein, Applicants respectfully request reconsideration and withdrawal of the objections and rejections set forth in the Office Action.

### I. Objections to Claims 10 and 11

Claim 10 is objected to because of an out of place comma following "trioxa-". Claim 10 has been amended to correct this.

Claim 11 is objected to because of the absence of commas separating the various compounds recited therein. Claim 11 has been amended to correct this.

### II. Rejection of Claims 1 and 11 Under 35 U.S.C. §112, Second Paragraph

Claims 1 and 11 are rejected under §112, second paragraph, as being indefinite.

According to the Office Action, the skilled artisan would not be apprised of the metes and bounds of the term "derivatives or fragments thereof having essentially the same binding function to biotin as avidin or streptavidin" in claim 1. Claim 1 has been amended to delete this language.

Claim 1 is also said to be indefinite because it is unclear what is encompassed by a linker defined as representing "ether, thioether or amine functionalities". The Examiner is unsure what it means to represent a functionality. Claim 1 has been amended to change the term "functionalities" to --groups--. Claim 4 has also been amended in this way.

Claim 11 is rejected because it is unclear what the compound at the top of the left side of page 6 in the claims filed January 26, 2005 is meant to convey. Claim 11 has been amended to delete this compound.

Applicants respectfully submit that amended claims 1 and 11 are not indefinite.

**III. Rejection of Claim 1 Under 35 U.S.C. §112, First paragraph**

Claim 1 is rejected under §112, first paragraph because the specification, while being enabling for specific trifunctional crosslinking moieties, is said to not reasonably provide enablement for all moieties which would fall within the scope of the genus described trifunctional crosslinking moieties.

Claim 1 has been amended to recite that the trifunctional crosslinking moiety, is an aromatic compound with 1,3,5 substitution. Support for this recitation can be found, e.g., in cancelled claim 21.

**IV. Rejection of Claims 1-5, 7, 9 and 21-24 Under 35 U.S.C. §112, First paragraph**

Claims 1-5,7, 9, and 21-24 are rejected under §112, first paragraph because the specification, while being enabling for specific toxin binding moieties, such as biotin, is said to not reasonably provide enablement for *any* toxic binding moiety.

Claim 1 has been amended to list specific toxin binding moieties. Support for this list can be found, e.g., in claim 3.

**V. Rejection of Claims 1-5, 7, 9-11 and 21-24 Under 35 U.S.C. §103(a), First paragraph**

Claims 1-5, 7, 9-11 and 21-24 are rejected under §103(a) as being unpatentable over Stayton in view of both Wilbur and Ribi.

Applicants respectfully submit that Stayton in view of Wilbur and Ribi would not have rendered instant claims 1, 3, 4, 7, 9-11 and 22-24 obvious.

Stayton teaches streptavidin molecules which contain a secondary functional domain. The secondary functional domain may, e.g., bind to a cell. It is well known that the streptavidin molecule is a tetrameric protein having four binding domains for biotin (see Ribi at col. 7, lines

23-29, and Example 3 in Stayton). Thus, the streptavidin molecule containing the secondary functional domain presents a penta-functional cross-linking moiety. In addition, Stayton teaches that the compound of interest, i.e., the compound to be bound to the secondary functional domain, should preferably be biotinylated (see col. 7, lines 40-42) and, thus, interact with (i.e., be able to bind to) the biotin binding domain of the streptavidin molecule. Therefore, a complex will be formed in which the biotin, the compound and the streptavidin molecule are bound to each other without any distance between the different components.

Stayton also teaches that the streptavidin molecules having a secondary functional domain may be immobilized onto a biotinylated substrate (col. 7, lines 50-64), contrary to the present invention, in which dibiotin compounds are bound to a substrate provided with avidin/streptavidin. By using the information obtained from Stayton, several embodiments can be envisaged:

(1) streptavidin molecules which have been bound to one biotin;

(2) streptavidin molecules which have been bound to two biotin molecules;

(3) streptavidin molecules which have been bound to three biotin molecules;

(4) streptavidin molecules which have been bound to four biotin molecules; and

(5) streptavidin molecules which have been bound to different numbers of biotin molecules.

However, Stayton does not teach or suggest anything about a method of conditioning an extracorporeal device, as acknowledged in the Office Action. Furthermore, Stayton teaches nothing regarding the creation of a structural network between avidin/streptavidin and the reagent or how such a network could be achieved by using the streptavidin molecule, compound and biotin mentioned in Stayton.

Wilbur teaches biotin compounds which may be monomers as well as dimeric, trimeric or multimeric biotin compounds. In a biotin dimer, it is important that the distance between the two biotin moieties is long enough (more than 15 angstroms) to bind two proteins, but short enough (less than 20 angstroms) that the two biotins will not bind to the same avidin or streptavidin

molecule (see page 29, lines 15-17). However, in the case of a biotin trimer, the distance between the biotin moieties is preferably from about 20 to about 60 angstroms, because such a distance ensures that the reagent will bind two binding sites on one and the same avidin bead. If the distance is less than 20 angstroms, only one biotin on the reagent can bind to one avidin bead in the device. The device is used to remove unbound reagents from the mammalian body fluid. If there is only one biotin bound to avidin in the device, the binding between the reagent and avidin is weaker compared to when two biotins have been bound to two binding sites on one avidin bead. If the distance is too short, i.e., the binding is weak, the reagent can easily be removed from the avidin and retransferred into the mammalian body fluid from which it was supposed to be removed. However, if the distance is more than 60 angstroms, the reagent will be bound to two avidin beads and crosslinking the avidin beads to each other. In that way, the physical property of the device containing the avidin beads will be altered and the flow through the device reduced. Thus, the optimal distance is between about 20 and about 60 angstroms.

Wilbur does not teach or suggest a method of conditioning an extracorporeal device or how to establish a structural network between the reagent and the device, which is possible to create with the reagent used in Applicants' claim 1 method.

Ribi teaches that it is known that biotin surfaces may comprise avidin and streptavidin. However, one skilled in the art faced with the problem of conditioning an extracorporeal device by the use of a reagent having a specific structure, wherein the specific structure enables the reagent to become immobilized in such a way that the two biotin molecules (dimer) of the reagent bind to a single molecule of streptavidin or avidin, and wherein the biotin molecules in the dimer are separated by a specific distance of 20 to 60 angstroms through two linkers in order to enable the binding of the two biotin moieties to one and the same avidin or streptavidin molecule, hence leaving the toxic binding moiety free to bind to a toxic material, would not gain any knowledge from Ribi. The toxin binding moiety involved in the present invention is separated from the biotin dimer by the three linkers and the trifunctional cross-linking moiety, contrary to the teaching of Ribi.

Furthermore, a person skilled in the art faced with the problem of conditioning an avidin coated device as set forth in claim 1 would not be guided by the combined teachings of Stayton, Ribi and Wilbur. On the contrary, Stayton teaches that the compound (toxin binding moiety)

should preferably be bound to biotin, and biotin and the compound together bind to streptavidin. The different embodiments described above relative to Stayton, which may be envisaged from Stayton's disclosure, are numeroud, and one skilled in the art would not be motivated to pick out any specific one of these embodiments due to the lack of guidance in solving the problem solved by the present invention. There is no indication in Stayton of any specific embodiment wherein streptavidin bound to two biotin molecules should be the best choice for practicing the present invention. If one skilled in the art would pick out such a specific embodiment by coincidence, it should preferably be one in which biotin is bound to the second functional domain (see Stayton at col. 7, lines 40-42), and one skilled in the art would not be motivated to introduce any of the linkers mentioned in Wilbur. Even in the case where one would introduce such linkers, there would be no scientific justification that the distance between the biotin molecules of a biotin dimer should be 20 to 60 angstroms, a distance that is important to enable the possibility for the biotin dimer of the reagent to bind to one and the same immobilized avidin or streptavidin molecule, and thereby create a structural network without intermolecular cross-linking in an extracorporeal device as set forth in Applicants' claim 1 method.

Thus, none of the references cited in the Office Action addresses the question of making adsorbent matrices in such a way that the original crosslinking properties are retained. One skilled in the art, reviewing the references, would have to engage in undue experimentation and guessing to arrive at Applicants' claimed method, including choosing tracks which are not said to be preferred in the references, e.g., introducing linkers or a specific length of the linkers when using dimers of biotin or having a specific structure of the reagent to be able to create a network in an extracorporeal device. There is no clear link or guidance between the cited references, and no motivation, reason or suggestion for one skilled in the art to combine the references to arrive at Applicants' claimed method. Specifically, none of the cited references addresses questions or solves problems that are relevant to arrive at the present invention without undue burden.

Therefore, for at least the foregoing reasons, Applicants respectfully submit that Stayton in view of Wilbur and Ribi would not have rendered instant claims 1, 3, 4, 7, 9-11 and 22-24 obvious.

## VI. Conclusion

In view of the amendments and remarks herein, Applicants respectfully request that the objections and rejections set forth in the Office Action be withdrawn and that claims 1, 3, 4, 7, 9-11 and 22-24 be allowed.

If any additional fees under 37 C. F. R. §§ 1.16 or 1.17 are due in connection with this filing, please charge the fees to Deposit Account No. 02-4300, Order No. 033700.004.

Respectfully submitted,
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Dated: December 5, 2005

Enclosures: (1) Petition for Extension of Time
(2) Check for the sum of $1020